Annual Reporting Form for SCEDDBO Projects and Cores

Administrative Core

Period covered by the report: 5/1/2007 – 4/30/2008
EPA Agreement Number: RD83329301-0
Investigators: Marie Lynn Miranda, Richard Auten, Sherman James, Pamela Maxson
Project Period: Year 1

Objectives of Core
The Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO) is governed through an Administrative Core that includes an Executive Committee composed of the Director, the two Co-Directors, and the Project Manager; an Internal Steering Committee composed of members of the Executive Committee and the Directors of the Research Projects and the Facility and Community Outreach Cores, as well as a community member and the Director of the Durham County Health Department; and an External Advisory Committee composed of senior environmental health scientists, as well as community representatives, with expertise relevant to SCEDDBO, who provide informal consultation, as well as annual formal evaluation of Center research and outreach activities.

The specific aims of the Administrative Core are to:

a. Provide scientific direction and leadership;
b. Coordinate and foster interactions among research project and facility core investigators;
c. Provide administrative services for the Center;
d. Direct the Young Investigators program; and
e. Represent Duke's SCEDDBO to the university, the community, the NIH, other Children's Environmental Health Centers across the United States, and the policy and scientific community interested in children's environmental health more broadly.

In all activities, SCEDDBO emphasizes the importance of diversity. The decision to focus on health disparities, the gender and racial diversity of Center leadership, the incorporation of natural, social and biomedical scientists, a commitment to community-based participatory research, and efforts to promote the careers of promising new investigators are all indicative of the importance that we place on fostering environments where all people can prosper.

Progress Report/Summary of Accomplishments
Announcement. The Administrative Core (AC) served as the host for Administrator Johnson when he traveled to Durham to announce the SCEDDBO award. AC personnel worked with Nicholas School and Duke University Offices of Communication and Government Relations to ensure that all substantive and organizational requests from the Administrator's office were fulfilled. A research roundtable allowed SCEDDBO investigators to brief the Administrator on scientific goals and objectives, as well as potential policy applications. The Administrator in turn provided helpful comments on the direction of the center. In addition, a formal event was held on campus, where Administrator Johnson, Stanley Meiburg (EPA), Richard Brodhead (President, Duke University), and Marie Lynn Miranda (PI, SCEDDBO) all offered remarks, followed by Q&A from the audience.

Project A: Mapping Disparities in Birth Outcomes

Period covered by the report: 5/1/2007 – 4/30/2008
EPA Agreement Number: RD83329301-0
Investigators: Marie Lynn Miranda (PI), Alan Gelfand, Sherman James, Pamela Maxson, Geeta Swamy
Project Period: Year 1

Objectives of Research

Project A utilizes the conceptual framework of the "weathering hypothesis," which posits that chronic and persistent stressors lead to accelerated biological aging of women, which in turn accounts for adverse birth outcomes among certain subpopulations. The central objective is to determine whether and to what extent joint exposures to socioeconomic and environmental stressors contribute to racial and ethnic health disparities in fetal growth restriction.

Using a geographically-based nested study design moving from analysis of births for the entire State of North Carolina to six demographically and geographically distinct counties to a single health center and state-of-the-art Geographic Information Systems applications with Bayesian spatial hierarchical modeling and other advanced spatial statistical approaches, the specific aims are to:

1. Spatially link detailed birth record, fetal death certificates, socioeconomic, environmental, tax assessor, community-based, and clinical obstetric data at highly resolved scales for the State of North Carolina from 1990-2003;
2. Refine the concept of fetal growth restriction by a) developing a joint distribution for birthweight and gestation using bivariate modeling for live births and fetal deaths – both separately and jointly, and b) defining it in terms of fetal and infant mortality, rather than percentile cut points; and
3. Determine whether and to what extent differential exposures to both environmental and social stressors help explain health disparities in fetal growth restriction among a) African-American women compared to Non-Hispanic white and Hispanic women, b) Older African-American women compared to younger African-American women, c) Hispanic women compared to Non-Hispanic white and African-American women, and d) Foreign born Hispanic women compared to US born Hispanic women.

This project evaluates a large number of factors in diverse populations, providing broad relevance for birth outcomes across time, space, and demography. Identifying social and environmental factors contributing to fetal growth restriction will improve our understanding of disease etiology and explain the racial disparity in disease incidence, leading to effective interventions against poor outcomes in all population groups.

Progress Report/Summary of Accomplishments

Over the past year, the Project A research team has met weekly to discuss new research ideas, review progress of current analysis and identify next steps, and work on manuscript preparation.

We have done considerable methodological work on how to *synthesize categorical datasets* to enhance inference. We are particularly interested in how to deal with a collection of datasets of varying sizes that are all relevant to a particular scientific question, but which include different subsets of the relevant variables, with some overlap. This work attempts to synthesize cross

classified categorical datasets drawn from a common population where many of the sets are incomplete (i.e., one or more of the classification variables is unobserved), but at least one is completely observed. This is expected to reduce uncertainty about the cell probabilities in the associated multi-way contingency table as well as for derived quantities such as relative risks and odds ratios. We have made substantial progress on the underlying modeling and have developed a simulation example as well. A manuscript on this work is presently in submission.

Out of efforts to develop new spatial methodologies for addressing health disparities, additional methodological work on *disaggregated spatial modeling for areal unit categorical data* is currently underway. This work uses innovative statistical methodology that extends spatial disease mapping techniques to model subgroups within areal units using a spatially smoothed, multilevel loglinear model. A presentation based on this work was given at the annual meeting of the American Public Health Association in November 2007, and a related manuscript is presently in submission. We are also exploring the public health applications of this methodology to elucidate health disparities across space and subgroups.

We have spent considerable time linking the detailed birth record data to USEPA PM_{10}, $PM_{2.5}$, and ozone monitoring data in order to study the impact of *maternal exposure to air pollution* on birth weight. We are especially focused on refining exposure metrics to most effectively characterize meaningful exposures, as well as to capture any windows of vulnerability. Significant progress has been made on the relationship between birth outcomes and exposure to particulate matter and ozone separately, and the current focus is determining how to characterize joint exposure to both particulate matter and ozone.

Our project on *racial residential segregation* is in an earlier stage of development, but promises to reveal key insights into how to think about the spatial aspects of the social factors influencing health disparities. We are working to determine which facets of segregation best characterize the way community-level racial residential segregation acts to promote health disparities in birth outcomes. Although our initial efforts were statewide, we have since decided that, given the significantly more detailed data available for Durham County, we will focus on this area while we work to determine what variables are most important to characterizing racial residential segregation in terms of its health consequences.

In addition, we have been working on specific analysis and manuscripts examining the impact of maternal age and birth order on birth weight, the joint distribution of birth weight and gestational age, and etiology of racial disparities in maternal hypertensive disorders.

Future Activities

We recently began the process of linking participants in Project B with their associated birth certificate record. We are excited to begin exploring the additional insights into the detailed birth record data that can be gleaned by linking these data with the rich dataset collected in Project B. This linkage will not only allow us to explore issues of data accuracy in the detailed birth record, but will also allow us to begin implementing the methods of synthesizing categorical data discussed above.

Publications

Tassone, E., Miranda, ML., Gelfand, A. Disaggregated Spatial modeling for Areal Unit Categorical Data. In submission.

Miranda, ML., Bhattacharya, S., Swamy, G., Gelfand, A. Synthesizing Categorical Datasets to Enhance Inference. In submission.

Supplemental Keywords
Data fusion, meta analysis, disparities, spatial disaggregation, spatial interpolation, spatial modeling

Research Project B: *Healthy Pregnancy, Healthy Baby: Studying Racial Disparities in Birth Outcomes*

Period covered by the report: 5/1/2007 – 4/30/2008
EPA Agreement Number: RD83329301-0
Investigators: Redford Williams (PI), Allison Ashley-Koch, Christina Gibson-Davis, Pamela Maxson, Marie Lynn Miranda, Jerome Reiter, Geeta K. Swamy,
Project Period: Year 1

Objectives of Research

The central objective of the Healthy Pregnancy, Healthy Baby Study is to determine how the interaction of environmental, social, and host factors contributes to disparities in birth outcomes between African-American and white women in the American South. There are four specific aims:

1. Conduct a cohort study of pregnant women in Durham, NC designed to correlate birth weight, gestation, and birth weight x gestation with environmental, social, and host factors;
2. Develop community-level measures of environmental and social factors by inventorying neighborhood quality and the built environment in partnership with local community groups;
3. Create a comprehensive data architecture, spatially resolved at the tax parcel level, of environmental, social, and host factors affecting pregnant women by linking data from the cohort study and neighborhood assessments with additional environmental and socioeconomic data; and
4. Determine whether and to what extent differential exposures explain health disparities in birth outcomes by applying innovative spatial and genetic statistical methods to:
    a. Identify environmental, social, and host factors that cluster to predict birth outcomes in the entire sample,
    b. Determine whether these clusters are more or less present in African-American versus white populations and quantify the proportion of health disparities explained by differences in cluster frequency, and
    c. Identify environmental, social, and host factors that cluster to predict birth outcomes within the African-American and white sub-samples and compare these clusters across racial groups.

Progress Report/Summary of Accomplishments

As of 4/1/08, 933 women have been enrolled in the study, with only 46 women withdrawn or lost to follow-up. Women are recruited from Duke University Medical Center (DUMC) and Lincoln Community Health Center. Demographic data indicate that we are successfully recruiting women who are most at risk for adverse pregnancy outcomes, particularly low-income, low educational attainment, and non-Hispanic black women.

The following information is collected from participants in the Healthy Pregnancy, Healthy Baby Study:

- Psychosocial measures include: CES-D, perceived stress, self-efficacy, interpersonal support, paternal support, perceived racism, perceived community standing, pregnancy intention, John Henryism Active Coping Scale, NEO Five Factor Inventory of personality.
- Environmental exposure survey measures include: short survey on fish consumption, smoking pattern and exposure to second-hand smoke, and drinking water source.
- Maternal and neonatal medical record abstraction includes: detailed pre-pregnancy medical and social history, antepartum complications, birth outcomes, and neonatal complications.
- Blood samples for genetic and environmental analysis to assess candidate genes related to environmental contaminant (nicotine, cotinine, cadmium, lead, mercury, arsenic, and manganese) metabolism, inflammation, vascular dysfunction, and stress response.
- Cord blood and placental samples are currently being stored for future genetic analysis and evaluation of activity at the maternal-fetal interface.

We have been highly successful in collection of participant-level data as well as biological samples, with greater than 90% attainment of maternal blood sample for genetic and environmental analyses. Collection of cord blood and placental samples, which began in June 2007, has also been successful with approximately 150 delivery samples collected.

All maternal data is georeferenced (i.e., linked to the physical address of the mother) using Geographic Information System (GIS) software. The Healthy Pregnancy/Health Baby Study also includes an in-depth neighborhood assessment designed to capture both built environment and community-level social stressors and community resources. The cohort study and neighborhood assessment data are spatially linked to extensive environmental and demographic data at a highly resolved spatial scale.

To date, we have generated genotypes on 624 blood samples from pregnant women for 104 Single Nucleotide Polymorphisms (SNPs) in sixteen genes, primarily involved in either metabolism of heavy metals or immune response.

Future Activities

In the upcoming year, we will continue to enroll study participants with our target sample size of 1500 pregnant women.

We will begin preliminary analyses on approximately 700 – 800 participants with complete pregnancy data, genetic results, and environmental results. Analyses will look at the joint impact of environmental, social, and host factors on birth outcomes, especially as they differ by race. Identification of such co-exposures could lead to development and implementation of strategies to prevent adverse birth outcomes, ultimately decreasing or eliminating the racial disparity.

Maternal blood samples will be analyzed for both protein and genetic associations with adverse birth outcomes. Maternal samples collected at 24 – 28 weeks gestation will be analyzed for protein levels involving markers of inflammation, vascular dysfunction, and stress response. DNA analysis is well underway with genotyping completed for several genetic polymorphisms regarding environmental contaminant metabolism as well as inflammatory cytokines and chemokines. Genotyping will continue and include genes involved in the maternal stress response and vascular/endothelial cell dysfunction. Statistical analysis regarding candidate gene polymorphisms will begin in June 2008. We will continue to genotype SNPs in the candidate genes we had proposed, as well as genotyping new, pertinent genes as the literature

suggests (i.e. GRK2/GRK5 as described by Liggett et al., 2008). In addition, during year 2, we will begin genotyping functional polymorphisms such as the 5HTTLPR in the serotonin transporter.

Publications
We are currently in the enrollment and data collection phase of the study but have begun to perform preliminary analyses.

Supplemental Keywords
Pregnancy, preterm birth, low birth weight, racial disparity, African American, environmental stressors, gene-environment interactions, psychosocial stressors, genes, single nucleotide polymorphisms

Project C: Perinatal Environmental Exposure Disparity and Neonatal Respiratory Health

Period covered by the report: 5/1/2007 – 4/30/2008
EPA Agreement Number: RD83329301-0
Investigators: Richard Auten (PI), W. Michael Foster
Project Period: Year 1

Objectives of Research: Specific Aims

1. To determine whether maternal exposure to airborne particulates (PM) and/or ozone (1st hit) restricts fetal growth and/or postnatal growth, and impairs lung development/function in newborn mice;
2. To determine whether PM and/or ozone exposure 're-programs' maternal inflammatory responses;
3. To determine whether postnatal (2nd hit) ozone exposure further impairs postnatal somatic and lung development/function following maternal PM and/or ozone exposures;
4. To determine whether genetic or developmental susceptibility to airway hyperreactivity exacerbates maternal and/or postnatal exposure effects on postnatal somatic and lung development/function.

Progress Report/Summary of Accomplishments
1. We have determined that postnatal ozone (1 ppm x 3h/d, 3 d/week x 4 weeks) significantly impairs postnatal weight gain in C56BL/6 mice. *Air pollutant exposure at a vulnerable window of postnatal development impairs growth*.
2. Postnatal ozone increases nebulized methacholine induced airway hyperreactivity (AHR) in C57BL/6 mice measured at 4 weeks but not 3 weeks. *Ozone induced AHR is developmentally regulated*.
3. We have found that prenatal instillation of particulate matter (St. Louis particle, NIST#1648) twice weekly in time mated pregnant mice augments postnatal ozone-induced AHR in mice, measured at 4 weeks postnatal. *Prenatal air pollutant exposure reprograms postnatal air pollutant responses that result in AHR*. A manuscript is in preparation to report these findings.
4. In studies just completed in collaboration with M. Ian Gilmour, EPA , we exposed time-mated C56BL/6 pregnant mice to internal combustion engine diesel exhaust (0.5, 1, & 2 mg/m^3 x 6h/d, 5d/week, from gestation day 6-17) v. air control. Pups delivered to exposed dams were

exposed postnatally to ozone as described above. Prenatal diesel exposure dose-dependently impaired lung compliance and pressure-volume loop hysteresis v. air or prenatal air postnatal ozone controls. There were parallel effects on nebulized methacholine challenge induced AHR. *Prenatal ambient exposures to diesel particulates at doses relevant to human environmental exposure worsened postnatal ozone-induced lung function and AHR*.

Future Activities

We have developed a recent collaboration with M. Ian Gilmour, US EPA, Research Triangle Park, NC to enable us to perform prenatal diesel particle exposures at concentrations and doses that more closely resemble human environmental exposures. Since the thrust of our project is to determine *combined* exposure effects on pregnancy and postnatal somatic and lung development, we are working on developing a system to perform simultaneous or alternating diesel and ozone exposures. This novel exposure scheme is now being developed and will being early in Year 2 of the project.

Major mechanistic questions underlie the link between prenatal exposure(s) and adverse neonatal outcomes. Since maternal inflammation is a mechanism central to many exposures implicated in fetal growth restriction, postnatal development, and postnatal morbidities, our plan is to test the concept by performing the single and combined pre- and post-natal exposures using inbred mouse strains with genetically determined but differing inflammatory repertoires in Year 2.

Publications

Brown J, Graham JA, Chen LC, Postlethwait EM, Ghio A, Foster WM, Gordon T. “Assessing Biological Plausability of Epidemiological Findings in Air Pollution Research.” *J Expos Sci Environ Epidem* 17:S97-105, 2007.

Supplemental Keywords

Airway hyperreactitivity, diesel exhaust particles, air pollution, lung function